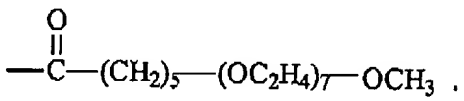
69. (New) The mixture according to claim 16, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 5 polyethylene glycol subunits.

70. (New) The mixture according to claim 16, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 7 polyethylene glycol subunits.

71. (New) The mixture according to claim 16, wherein at least one of the oligomers is covalently coupled to Lys^{B29} of the human insulin and has the formula:



Please cancel claims 4, 5, 6, 12-15, 31-39, 42-45, 49, 51, and 53-67 without prejudice or disclaimer.

Remarks

Claims 1-67 are pending in the present application. Applicants appreciate the indication that claims 40 and 41 are allowed. Applicants further appreciate the indication that claims 7, 16, 49, and 51 contain allowable subject matter.

Although Applicants traverse the rejections made in the February 24, 2003 Office Action, Applicants have chosen to present amendments herein to place the application in condition for allowance while retaining the right to pursue the cancelled claims in a separate application.

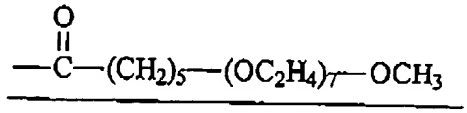
Applicants have also revised claims as suggested by the Examiner. Support for the proposed amendments to the claims can be found in the originally filed claims and/or the specification.

Any questions that the Examiner may have should be directed to Shawna Cannon Lemon, who may be reached at (919) 854-1400.

Confidentiality Note

Marked-up Version of Claims Incorporating Proposed Amendments

1. (Amended) A mixture of conjugates each comprising **[an]** a human insulin drug coupled to an oligomer **[that comprises a polyethylene glycol moiety,]** having a formula:



wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

n is the number of different molecules in the sample;

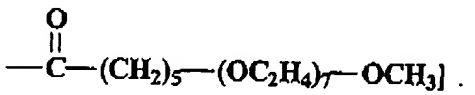
N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule.

2. The mixture according to Claim 1, wherein the dispersity coefficient is greater than 100,000.

3. The mixture according to Claim 1, wherein the dispersity coefficient is greater than 500,000.

7. (Amended) The mixture according to Claim 1, wherein the **[insulin drug is human insulin and the]**oligomer is covalently coupled to Lys^{B29} of the human insulin **[and has the formula:**



] .

8. The mixture according to Claim 1, wherein the mixture has an *in vivo* activity that is greater than the *in vivo* activity of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

9. The mixture according to Claim 1, wherein the mixture has an *in vitro* activity that is greater than the *in vitro* activity of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

10. (Amended) The mixture according to Claim 1, wherein the **[mixture]** human insulin-drug oligomer has an increased resistance to degradation by chymotrypsin when compared to the resistance to degradation by chymotrypsin of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

11. The mixture according to Claim 1, wherein the mixture has an inter-subject variability that is less than the inter-subject variability of a polydispersed mixture of insulin drug-oligomer conjugates having the same number average molecular weight as the mixture.

16. (Amended) A mixture of conjugates each comprising insulin coupled to an oligomer that comprises a polyethylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

M_i is the mass of the i^{th} molecule; and

wherein the conjugate comprises a first oligomer and a second oligomer; and

[The mixture according to Claim 15]

wherein the first oligomer is covalently coupled at Lys^{B29} of the insulin and the second oligomer is covalently coupled at N-terminal A1 or N-terminal B1 of the insulin.

17. The mixture according to Claim 1, wherein the insulin drug is covalently coupled to the oligomer.

18. (Amended) The mixture according to Claim [1] 16, wherein the insulin [drug] is covalently coupled to at least one of the [oligomer] oligomers by a hydrolyzable bond.

19. (Amended) The mixture according to Claim [1] 16, wherein the insulin is covalently coupled to the polyethylene glycol moiety of at least one of the [oligomer] oligomers.

20. (Amended) The mixture according to Claim [19] 16, wherein at least one of the [oligomer] oligomers [further] comprises a lipophilic moiety covalently coupled to the polyethylene glycol moiety.

21. (Amended) The mixture according to Claim [1] 16, wherein at least one of the [oligomer] oligomers [further] comprises a lipophilic moiety.

22. The mixture according to Claim 21, wherein the insulin drug is covalently coupled to the lipophilic moiety.

23. The mixture according to Claim 21, wherein the polyethylene glycol moiety is covalently coupled to the lipophilic moiety.

24. The mixture according to Claim 1, wherein the conjugate comprises a first oligomer and a second oligomer.

25. (Amended) The mixture according to Claim [24] 16, wherein the first and the second oligomers are the same.

26. (Amended) The mixture according to Claim [1] 16, wherein the oligomer comprises a first polyethylene glycol moiety covalently coupled to the insulin by a non-hydrolyzable bond and a second polyethylene glycol moiety covalently coupled to the first polyethylene glycol moiety by a hydrolyzable bond.

27. The mixture according to Claim 26, wherein the oligomer further comprises a lipophilic moiety covalently coupled to the second polyethylene glycol moiety.

28. (Amended) The mixture according to Claim [1] 16, wherein the conjugates are each amphiphilically balanced such that each conjugate is aqueously soluble and able to penetrate biological membranes.

29. A pharmaceutical composition comprising:
the mixture according to Claim 1; and
a pharmaceutically acceptable carrier.

30. (Amended) A method of treating insulin deficiency in a subject in need of such treatment, said method comprising:

administering an effective amount of the composition of claim 29 **[a mixture of conjugates each comprising an insulin drug coupled to an oligomer comprising a polyethylene glycol moiety, wherein the mixture has a dispersity coefficient (DC) greater than 10,000 where**

$$DC = \frac{\left(\sum_{i=1}^{n} N_i M_i\right)^2}{\sum_{i=1}^{n} N_i M_i^2 \sum_{i=1}^{n} N_i - \left(\sum_{i=1}^{n} N_i M_i\right)^2}$$

wherein:

n is the number of different molecules in the sample;

N_i is the number of i^{th} molecules in the sample; and

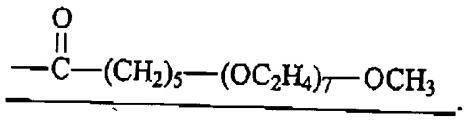
M_i is the mass of the i^{th} molecule;]

to the subject to treat the insulin deficiency.

40. A substantially monodispersed mixture of conjugates each comprising human insulin covalently coupled at Lys^{B29} of the human insulin to the carboxylic acid moiety of a carboxylic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol moiety having at least 7 polyethylene glycol subunits

41. The substantially monodispersed mixture according to Claim 40, wherein the conjugates each consist of human insulin covalently coupled at Lys^{B29} of the human insulin to the carboxylic acid moiety of hexanoic acid, which is covalently coupled at the end distal to the carboxylic acid moiety to a methyl terminated polyethylene glycol moiety having 7 polyethylene glycol subunits.

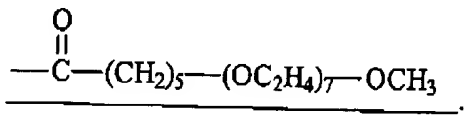
46. (Amended) A mixture of conjugates each comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons, wherein the insulin drug is human insulin and each oligomer is covalently coupled to Lys^{B29} of the human insulin and has the formula:



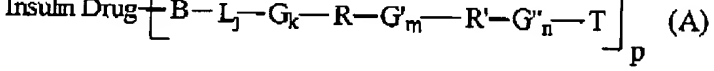
47. The mixture according to Claim 46, wherein the standard deviation of the molecular weight distribution is less than about 14 Daltons.

48. The mixture according to Claim 46, wherein the standard deviation of the molecular weight distribution is less than about 11 Daltons.

50. (Amended) A mixture of conjugates each comprising an insulin drug coupled to an oligomer that comprises a polyethylene glycol moiety, said mixture having a molecular weight distribution with a standard deviation of less than about 22 Daltons, in which each conjugate[:] comprises an insulin drug coupled to an oligomer[;] and has the same number of polyethylene glycol subunits, wherein the insulin drug is human insulin and each oligomer is covalently coupled to Lys^{B29} of the human insulin and has the formula:



52. (Amended) A mixture of conjugates in which each conjugate is the same and has the formula:



(A)

wherein:

B is carbonyl;

L is a linker moiety;

G, G' and G" are individually selected spacer moieties;

R is C_5 alkylene and R' is polyethylene glycol having 7 polyethylene glycol subunits **[R is a lipophilic moiety and R' is a polyalkylene glycol moiety, or R' is the lipophilic moiety and R is the polyalkylene glycol moiety]**;

T is methoxy;

J[, k, m and n are individually] is 0 or 1;

k, m and n are 0; and

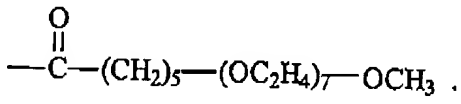
p is an integer from 1 to the number of nucleophilic residues on the insulin drug.

68. (New) The mixture according to claim 16, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 2 polyethylene glycol subunits.

69. (New) The mixture according to claim 16, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 5 polyethylene glycol subunits.

70. (New) The mixture according to claim 16, wherein at least one of the oligomers comprises a polyethylene glycol moiety having at least 7 polyethylene glycol subunits.

71. (New) The mixture according to claim 16, wherein at least one of the oligomers is covalently coupled to Lys^{B29} of the human insulin and has the formula:



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